VIA MEDICA

REVIEW

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Short-acting inhaled β2-agonists: why, whom, what, how?

Abstract

We showed the present data about the efficacy and safety of inhaled short-acting β2-agonists (SABA), such as salbutamol and fenoterol, in the management of obstructive diseases in children and adults. Our work discusses major mechanisms of action, clinical effects, possible side effects and indications of inhaled SABA. We presented current recommendations for the position of SABA in the therapy of obstructive diseases in children and adults, particularly in asthma and chronic obstructive pulmonary disease.

Key words: short-acting β2-agonist, salbutamol, fenoterol, inhalation, nebulization, asthma, COPD

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Introduction

Short-acting β2-agonists (SABA) stimulate β2-adrenergic receptor (β2-AR). They are called β2-mimetics or β2-agonists. First selective SABA widely used in clinical practice appeared more than 50 years ago. They were introduced to the global market in the following order: terbutaline (1966 yr.), salbutamol (1968 yr.) and fenoterol (1970 yr.) [1]. Next drugs, such as levalbuterol, reproterol, rimiterol, klenbuterol and pirbuterol, were introduced afterwards [2–4]. Short-acting β2-agonists are selective agonists of β2-AR, however they differ in their degree of selectivity. Salbutamol (albuterol) is the most used SABA in the world — in US it took 9th place on the list of prescribed medicines in 2016 (70 million of prescriptions) [5]. According to World Health Organization (WHO) salbutamol ranks among the most effective and safest medicines essential to health care systems [6]. Racemic salbutamol is an equal (1:1) mixture of R-salbutamol (levalbuterol) and S-salbutamol isomers. R-isomer of salbutamol is a pharmacologically active compound which exhibits many clinical effects, including potent bronchodilation [7]. Suppression of bronchoconstriction and bronchodilation occur 5 minutes after administration of inhaled salbutamol, but the duration of action does not exceed 4–6 hours (Figure 1) [8].

Drugs from this group provide effective protection against exercise-induced bronchoconstriction within 0.5–2.0 hours also against bronchoconstriction triggered by exposure to sensitizing allergen [9, 10]. Clinical studies show more potent bronchodilation and less side effects of R-salbutamol in comparison with racemic salbutamol [11–13]. High cost of levalbuterol justifies, however, its administration only in selected clinical conditions [13].

Salbutamol *versus* fenoterol

Two inhaled drugs from SABA group are available in Poland: salbutamol and fenoterol. Table 1 shows their most important properties.

Data in the table demonstrate that β2/β1 (selectivity index) stimulation index is 10 times greater for salbutamol than fenoterol. Having in mind similar stimulation of β2 receptors by both drugs (0.55 salbutamol *vs* 0.60 fenoterol), it means that salbutamol exerts more selective β2-AR stimulation *vs* fenoterol and both cause similar bronchodilation. Studies from the 1990s

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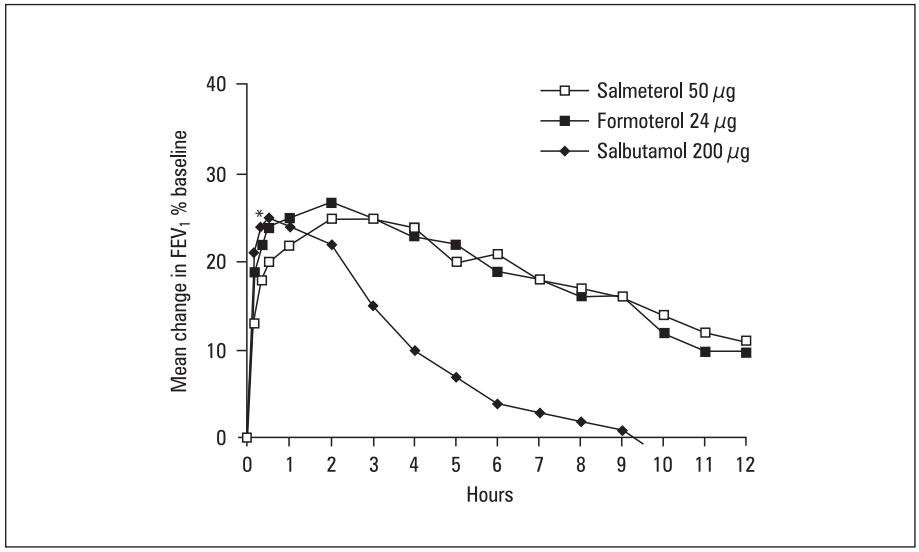

Figure 1. Effect of single dose of salbutamol, formoterol, and salmeterol on FEV_1 value in asthma patients [8].
FEV_1 — forced expiratory volume in the first second

Table 1. Comparison of short-acting β2-agonists' (salbutamol and fenoterol *vs* isoproterenol) ability to stimulate β-adrenergic receptors (β1, β2, β3) [14, 15]

	β1 inotropic activity (atrium)	β2 dilatory activity (bronchi)*	β3 lipolytic activity (adipocytes)	β2/β1 index
Isoproterenol	1,0	1,0	1,0	1,0
Salbutamol	0,0004	0,55	0,002	1375
Fenoterol	0,005	0,6	0,02	120

*Increase in FEV_1 (forced expiratory volume in the first second) ≥ 15% from baseline

proved similar or better clinical efficacy and better safety of salbutamol in comparison with inhaled fenoterol in different age groups of asthma patients [16, 17]. Better safety is also a result of the fact that salbutamol shows more features of β2-AR partial agonist than fenoterol. It determines that asthma patients using salbutamol have lower risk of death *vs* patients using fenoterol [17, 18]. It should be stressed that adverse effects of fenoterol increase in hypoxemia, which occurs during severe and prolonged episode of bronchoconstriction [19].

Clinical effects of SABA

Short-acting β2-agonists in conditions with bronchoconstriction exert many following clinical effects [1, 15]:

— bronchodilation (removal of bronchial smooth muscles constriction);
— prevention of bronchoconstriction induced by different bronchoconstrictive factors;
— reduction of capillary permeability (reduction of plasma exudate);
— suppression of sensory nerves activation;
— improvement of mucociliary clearance;
— dilatation of pulmonary vascular bed (decrease in pO_2);
— increased release of surfactant.

They can depend on the polymorphism of gene encoding β2-AR located on chromosome 5q31-q32 [20, 21]. Some studies showed relationship between response to SABA, course of asthma and the polymorphism of gene encoding β2-AR [22]. It is mainly about 2 polymorphisms: genotype Arg/Arg at codon 16 of gene encoding β2-AR and Gln/Gln at codon 27 of this gene. It was revealed that homozygotes for Arg/Arg at codon 16 of gene encoding β2-AR with chronic obstructive pulmonary disease (COPD) are predisposed to more severe clinical course of the disease [23]. Similar relationship was shown in patients with cystic fibrosis with altered response to SABA [24].

Short-acting β2-agonists usage can be associated with many side effects described may years ago [25]: tachycardia, skeletal muscle tremor, hypokalaemia, increased level of lactic acid in plasma (lactic acidosis), headaches, hyperglycaemia. Systemic side effects are observed rarely after inhalation administration and increased risk of cardiovascular side effects appear in patients with comorbid cardiovascular disease, especially in the elderly [26, 27]. It is worth mentioning that paradoxical bronchoconstriction after inhalation of SABA occurs in 4.4% of the general population [28].

There are additional possible side effects and adverse clinical effects when SABA are used in asthma. These effects occur in patients receiving SABA as monotherapy or/and if SABA are used very often or regularly without inhaled corticosteroids (ICS). It can lead to increased risk of the following adverse outcomes [29–35]:

— decrease in the number and sensitivity of β2-AR;
— diminished bronchial response to SABA or/ /and LABA;
— increased bronchial hyperresponsiveness;
— increased allergic reactions and eosinophilic airway inflammation;
— increased risk for asthma exacerbation (with regular or frequent use: ≥ 3 SABA canisters/ /year, average 1.7 puffs/day);
— increased risk of death in patients with asthma (≥ 11 SABA canisters/year);
— deterioration in spirometric parameters.

These facts which are known for many years and other new clinical evidences for efficacy and safety of SMART therapy (Single Maintenance and Reliver Therapy) changed the perception of the role and place of SABA in the management of asthma in last Global Initiative for Asthma report (GINA) 2019 [36], which will be discussed further below. Another way of limiting the SABA overuse relies on monitoring use of SABA by patients preferably with electronic inhalers [37, 38], including inhalers transmitting information to the health care system in real time [39].

Salbutamol in pressurised metered-dose inhaler in comparison to other pharmaceutical forms of SABA

Short-acting β2-agonists have different routes of administration (inhalation, oral and intravenous), because they are available in different pharmaceutical forms. Many forms of salbutamol are available [40]:

— inhalation aerosol (suspension) from pressurised metered-dose inhaler (pMDI) (children and adults);
— powder from dry powder inhaler (DPI), types: Diskus (children over 4 years and adults), Turbuhaler (children over 3 years and adults) and Easyhaler and (children over 4 years, adults);
— inhalation solution for nebulizers (children and adults);
— sirup (children over 2 years, adults);
— tablets (children over 2 years, adults);
— solution for injection (adults).

Inhalation is the most effective way of SABA therapy in airway diseases. Oral therapy can be alternative only exceptionally in small children, who do not accept inhalation or cannot inhale properly [38]. Additional parenteral therapy (salbutamol) is necessary rarely in patients with severe exacerbation of asthma, who do not respond do proper inhalation therapy [41].

Inhalation formulations of SABA most often used are listed in Table 2 [43].

According to table 2, four inhalation formulations of salbutamol are available: pMDI, pressurised metered-dose inhaler — breath actuated pMDI (pMDI-BA), DPI and inhalation solution for nebulizers; fenoterol is available only as pMDI. The expected therapeutic clinical effects and probability of side effects can depend on the choice of SABA inhalation method. Below we present the most important rules of SABA inhalation therapy:

Table 2. Inhalation formulations of SABA and SABA/ipratropium bromide combinations. Abbreviations according to [44]

Type of inhaler	pMDI	pMDI-BA	MDLI (respimat)	DPI	Nebulization
Salbutamol	+	+	–	+	+
Fenoterol	+	–	–	–	–
Salbutamol + ipratropium bromide	+*	–	+	–	+
Fenoterol + ipratropium bromide	+	–	+	–	+

pMDI — pressurised metered-dose inhaler; pMDI-BA — pressurised metered-dose inhaler — breath actuated); MDLI — metered dose liquid inhaler; DPI — dry powder inhaler

1. pMDI with properly fitted inhalation chamber is preferred method of SABA inhalation in children below 6 years, irrespective of severity of asthma attack, place of administration (home, admission ward, clinical ward, intensive care unit) [36, 45, 46].
2. Dose of salbutamol from pMDI depends mainly on the severity of asthma attack, not on patient age. According to GINA 2019 report during the first hour children below 6 years can receive up to 6 puffs, older children and adults can receive up to 12–30 puffs [36].
3. Salbutamol can be inhaled from DPI (e.g: Diskus and Easyhaler) in children above 6 years and adult with asthma, which provides similar clinical efficacy to pMDI [36]. Studies on administration of salbutamol from other DPI are ongoing [47].
4. Nebulization with pneumatic nebulizer — both intermittent and continuous — should be used in case of insufficient response or lack of response to SABA and life-threatening bronchoconstriction [36, 48, 49]. In adults with severe exacerbation of asthma continuous nebulized salbutamol more effectively improves lung function than intermittent nebulization [50].
5. Clinical effects of salbutamol nebulization to a considerable degree depend on the type of nebulizer: breath actuated pneumatic nebulizer provides better effect than continuous nebulization and mesh nebulizer in comparison to pneumatic nebulizer [51, 52].

Table 3. Current indications for SABA in children and adults [36, 55–64]*

Disease/state	Indications	Comment
Asthma	Attacks of dyspnoea, cough, and wheeze Disease exacerbations Prevention of exercise-induced bronchoconstriction Prevention of bronchoconstriction triggered by allergen exposure	Alternative to SMART therapy in patients < 12 years Always with ICS — evidence A
Obstructive bronchitis — so-called early childhood asthma	Exacerbation of bronchoconstriction	First-line treatment Number of doses should be adjusted to the patient's clinical condition
Stable COPD	Initial treatment — dyspnoea attack or/and respiratory difficulties As-needed SABA	— Only patients from group A — Reduction in symptoms and an increase in FEV_1 — evidence A — Combination of SABA + SAMA is superior to SABA or SAMA alone (symptoms and FEV_1) — evidence A
COPD — exacerbation	Acute exacerbation of disease SABA added to other medication	Increase the dose or frequency of SABA or combine SABA and SAMA in the initial treatment of acute exacerbation — evidence C
Bronchiolitis	Selected cases with confirmed positive clinical response to treatment	In most cases there are no indications to routine therapy
Cystic fibrosis	Pulmonary exacerbation with features of bronchoconstriction and confirmed positive clinical response or in patients with positive BDR test, before inhalation of hypertonic saline	Rather commonly used, however ecommendations are not explicit
Transient tachypnoea of the newborns		Very poor evidences for the efficacy
Chronic lung disease in premature babies	Prevention and treatment	Poor evidences for the efficacy
Familial dysautonomia	SABA + SAMA	1 study confirming SABA efficacy
Other diseases with reversible bronchoconstriction	Acute chest syndrome in sickle cell disease	Further studies are needed
Bronchodilator reversibility (BDR) test	Spirometric features of bronchoconstriction (FEV_1%FVC < 80 % predicted value, FEV_1%VC < 80% predicted value, PEF < 80% predicted value)	2–4 puffs of salbutamol pMDI + inhalation chamber as the standard of BDR test

*One shouldn't be afraid of administration of SABA (salbutamol) in the elderly (> 90 years) [65] FEV_1 — forced expiratory volume in the first second; ICS — inhaled corticosteroids; COPD — chronic obstructive pulmonary disease; SABA — short-acting β2-agonists; SAMA — short-acting muscarinic antagonists; SMART — Single Maintenance and Reliver Therapy

Table 4. Initial emergency (as-needed) pharmacotherapy of asthma according to GINA 2019 report [36]

Age group	Preferred management	Alternative management	Comments
Patients ≥ 12 years	Low dose ICS-formoterol — Step 1–5 treatment	SABA pMDI, pMDI-BA SABA pMDI + IC SABA DPI— Step 1–5 treatment	ICS: budesonide or beclometasone
Patients 6–11 years	SABA DPI SABA pMDI + IC SABA DPI — Step 1–5 treatment	Low dose ICS-formoterol — Step 3–5 treatment*	*Children receiving ICS-formoterol combination as maintenance
Patients 5 years and younger	SABA "as-needed" pMDI + IC — Step 1–4 treatment	SABA "as-needed" by nebulizer — Step 1–4 treatment	Proper use of the equipment and estimation of appropriate dose of the drug are required

DPI — dry powder inhaler; ICS — inhaled corticosteroids; IC — inhalation chamber; pMDI — pressurised metered-dose inhaler; SABA — short-acting β2-agonists

6. Parenteral, oral, or nebulized SABA are associated with increased risk of side effects (tachycardia, muscle tremor, headaches, hypokalaemia). In this respect inhalation from pMDI is the safest method [53, 54].
7. Short-acting β2-agonist (alternatively in combination with ipratropium bromide) in pMDI + IC or in nebulization is the first-line initial treatment of acute exacerbation of COPD [55]. Dose of SABA from pMDI: 1–2 puffs every hour for the first 2–3 hours of treatment, then 1–2 puffs every 2–4 hours depending on the response to the treatment [56].
8. Patients with COPD should receive air-driven nebulization of SABA, but not high-flow oxygen-driven nebulization to avoid hypercapnia in patients with chronic respiratory failure [57].

Indications to SABA

Short-acting β2-agonists have been very important drugs for many years used in the management of various bronchoconstrictive diseases in children and adults. Indications for their administration were collected in Table 3.

Current place of SABA in the management of asthma is defined by GINA 2019 report, which considerably changes former recommendations (tab. 4) [35]. Experts in this report do not recommend SABA monotherapy in all age groups (look tab. 3) because of patient's safety. Each SABA (regardless of its inhalation formulation) should be used simultaneously with ICS — from one or separate inhalers (or sometimes with oral/parenteral corticosteroid).

GINA 2019 report based on high-quality clinical studies recommends the following as-needed (emergency) step 1–5 treatment in patient ≥ 12 years: low dose ICS in combination with formoterol [36]. As-needed SABA from pMDI or DPI remains alternative option (worse regarding the efficacy and safety). In children 6–11 years preferred emergency management is administration of SABA from pMDI + inhalation chamber in combination with ICS (any medication) or oral corticosteroid [36]. Administration of SABA from pMDI + inhalation chamber: 4–10 puffs for every 20 minutes for the first hour of symptoms. Budesonide in combination with formoterol in SMART therapy model is alternative option for some children [36]. In group of children up to 5 years the only option of emergency treatment is SABA „as-needed" — from pMDI + inhalation chamber (preferred management) or in nebulization (alternative management) in all asthma steps [36].

References:

1. Tattersfield A.E. Current issues with beta2-adrenoceptor agonists: historical background. Clin Rev Allergy Immunol. 2006; 31(2–3): 107–118, doi: 10.1385/CRIAI:31:2:107, indexed in Pubmed: 17085787.
2. Baronti A., Grieco A., Vibelli C. A comparison between inhaled clenbuterol and salbutamol in chronic bronchitis with reversible airway obstruction. Eur J Respir Dis. 1980; 61(3): 143–150, indexed in Pubmed: 7002574.
3. Muittari A. A comparison of rimiterol and salbutamol by inhalation at high and low dose in asthmatic patients. Respiration. 1978; 35(3): 165–172, doi: 10.1159/000193873, indexed in Pubmed: 25466.
4. Rau J.L. Inhaled adrenergic bronchodilators: historical development and clinical application. Respir Care. 2000; 45(7): 854–863, indexed in Pubmed: 10926383.
5. Aitken M. Medicines Use and Spendingin the U.S. A Review of 2016 and Outlook to 2021. QuintilesIMS Instutite. 2017. Dostępne na stronie: https://structurecms-staging-psyclone.netdna-ssl.com/client_assets/dwonk/media/attachments/590c/6aa0/6970/2d2d/4182/0000/590c6aa069702d2d41820000.pdf. [dostęp: 12.08.2019].
6. World Health Organization. April 2015. Archived (PDF) from the original on 13 December 2016. Retrieved 8 December 2016.
7. Lipworth B.J., Clark D.J., Koch P. i wsp. Pharmacokinetics and extrapulmonary beta 2 adrenoceptor activity of nebulised racemic salbutamol and its R and S isomers in healthy volunteers. Thorax. 1997; 52(10): 849–852, doi: 10.1136/thx.52.10.849, indexed in Pubmed: 9404370.
8. van Noord J.A., Smeets J.J., Raaijmakers J.A. i wsp. Salmeterol versus formoterol in patients with moderately severe asthma: onset and duration of action. Eur Respir J. 1996; 9(8):

1684–1688, doi: 10.1183/09031936.96.09081684, indexed in Pubmed: 8866595.
9. Inman M.D., O'Byrne P.M. The effect of regular inhaled albuterol on exercise-induced bronchoconstriction. Am J Respir Crit Care Med. 1996; 153(1): 65–69, doi: 10.1164/ajrccm.153.1.8542164, indexed in Pubmed: 8542164.
10. Cockcroft D. Inhaled 2 -agonists and airway responses to allergen. J Allergy Clin Immunol. 1998; 102(5): S96–S99, doi: 10.1016/s0091-6749(98)70038-7.
11. Patel M., Thomson N.C. (R)-salbutamol in the treatment of asthma and chronic obstructive airways disease. Expert Opin Pharmacother. 2011; 12(7): 1133–1141, doi: 10.1517/14656566.2011.571210, indexed in Pubmed: 21453221.
12. Yuan J., Lu Z.K., Zhang Y. i wsp. Clinical outcomes of levalbuterol versus racemic albuterol in pediatric patients with asthma: Propensity score matching approach in a medicaid population. Pediatr Pulmonol. 2017; 52(4): 516–523, doi: 10.1002/ppul.23565, indexed in Pubmed: 27701831.
13. Yuan J., Lu K. Economic impact of levalbuterol versus albuterol in low-income population. Value Health. 2014; 17(7): A781, doi: 10.1016/j.jval.2014.08.376, indexed in Pubmed: 27202897.
14. Hochhaus G., Möllmann H. Pharmacokinetic/pharmacodynamic characteristics of the beta-2-agonists terbutaline, salbutamol and fenoterol. Int J Clin Pharmacol Ther Toxicol. 1992; 30(9): 342–362, indexed in Pubmed: 1358833.
15. Emeryk A., Lis G. B2-mimetyki w astmie. W: Astma i choroby obturacyjne oskrzeli u dziec. A. Emeryk, A. Bręborowicz, G. Lis (red.). Elsevier Urban&Partner. Wrocław 2010: 145–154.
16. Scalabrin D.M., Solé D., Naspitz C.K. Efficacy and side effects of beta 2-agonists by inhaled route in acute asthma in children: comparison of salbutamol, terbutaline, and fenoterol. J Asthma. 1996; 33(6): 407–415, doi: 10.3109/02770909609068185, indexed in Pubmed: 8968295.
17. Bremner P., Burgess C., Beasley R. i wsp. Nebulized fenoterol causes greater cardiovascular and hypokalaemic effects than equivalent bronchodilator doses of salbutamol in asthmatics. Respir Med. 1992; 86(5): 419–423, doi: 10.1016/s0954-6111(06)80009-0, indexed in Pubmed: 1462021.
18. Bremner P., Siebers R., Crane J. i wsp. Partial *vs* full beta-receptor agonism. A clinical study of inhaled albuterol and fenoterol. Chest. 1996; 109(4): 957–962, doi: 10.1378/chest.109.4.957, indexed in Pubmed: 8635377.
19. Bremner P., Burgess C.D., Crane J. i wsp. Cardiovascular effects of fenoterol under conditions of hypoxaemia. Thorax. 1992; 47(10): 814–817, doi: 10.1136/thx.47.10.814, indexed in Pubmed: 1481183.
20. Martinez F.D., Graves P.E., Baldini M. i wsp. Association between genetic polymorphisms of the beta2-adrenoceptor and response to albuterol in children with and without a history of wheezing. J Clin Invest. 1997; 100(12): 3184–3188, doi: 10.1172/JCI119874, indexed in Pubmed: 9399966.
21. NCBI NCBI Gene. 2019. Jul 23, [2018-11-19]. ADRB2 adrenoceptor beta 2 [Homo sapiens (human)]. Dostępne na stronie: www.ncbi.nlm.nih.gov/gene/154. [dostęp: 14.12.2019].
22. Hikino K., Kobayashi S., Ota E. i wsp. The influence of beta-2 adrenergic receptor gene polymorphisms on albuterol therapy for patients with asthma: protocol for a systematic review and meta-analysis. JMIR Res Protoc. 2019; 8(9): e14759, doi: 10.2196/14759, indexed in Pubmed: 31538939.
23. Emeryk-Maksymiuk J., Emeryk A., Krawczyk P. i wsp. Beta-2-adrenoreceptor polymorphism at position 16 determines the clinical severity of chronic obstructive pulmonary disease. Pulm Pharmacol Ther. 2017; 43: 1–5, doi: 10.1016/j.pupt.2017.01.005, indexed in Pubmed: 28093224.
24. Marson F.A.L., Bertuzzo C.S., Ribeiro A.F. i wsp. Polymorphisms in ADRB2 gene can modulate the response to bronchodilators and the severity of cystic fibrosis. BMC Pulm Med. 2012; 12: 50, doi: 10.1186/1471-2466-12-50, indexed in Pubmed: 22950544.
25. Lulich K.M., Goldie R.G., Ryan G. i wsp. Adverse reactions to beta 2-agonist bronchodilators. Med Toxicol. 1986; 1(4): 286–299, doi: 10.1007/bf03259844, indexed in Pubmed: 2878344.
26. Sears M. Adverse effects of -agonists. J Allergy Clin Immunol. 2002; 110(6): S322–S328, doi: 10.1067/mai.2002.129966.
27. Gupta P., O'Mahony M.S. Potential adverse effects of bronchodilators in the treatment of airways obstruction in older people: recommendations for prescribing. Drugs Aging. 2008; 25(5): 415–443, doi: 10.2165/00002512-200825050-00005, indexed in Pubmed: 18447405.
28. Schissler A.J., Celli B.R. Prevalence of paradoxical bronchoconstriction after inhaled albuterol. Respir Med. 2018; 141: 100–102, doi: 10.1016/j.rmed.2018.06.028, indexed in Pubmed: 30053954.
29. Hancox R.J., Cowan J.O., Flannery E.M. i wsp. Bronchodilator tolerance and rebound bronchoconstriction during regular inhaled beta-agonist treatment. Respir Med. 2000; 94(8): 767–771, doi: 10.1053/rmed.2000.0820, indexed in Pubmed: 10955752.
30. Drazen J.M., Israel E., Boushey H.A. i wsp. Comparison of regularly scheduled with as-needed use of albuterol in mild asthma. Asthma Clinical Research Network. N Engl J Med. 1996; 335(12): 841–847, doi: 10.1056/NEJM199609193351202, indexed in Pubmed: 8778601.
31. Stanford R.H., Shah M.B., D'Souza A.O. i wsp. Short-acting β-agonist use and its ability to predict future asthma-related outcomes. Ann Allergy Asthma Immunol. 2012; 109(6): 403–407, doi: 10.1016/j.anai.2012.08.014, indexed in Pubmed: 23176877.
32. Sears M.R., Lötvall J. Past, present and future--beta2-adrenoceptor agonists in asthma management. Respir Med. 2005; 99(2): 152–170, doi: 10.1016/j.rmed.2004.07.003, indexed in Pubmed: 15715182.
33. Suissa S., Ernst P., Boivin J.F. i wsp. A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. Am J Respir Crit Care Med. 1994; 149(3 Pt 1): 604–610, doi: 10.1164/ajrccm.149.3.8118625, indexed in Pubmed: 8118625.
34. Aldridge R.E., Hancox R.J., Robin Taylor D. i wsp. Effects of terbutaline and budesonide on sputum cells and bronchial hyperresponsiveness in asthma. Am J Respir Crit Care Med. 2000; 161(5): 1459–1464, doi: 10.1164/ajrccm.161.5.9906052, indexed in Pubmed: 10806139.
35. Aldridge R.E., Hancox R.J., Cowant J.O. i wsp. Eosinophils and eosinophilic cationic protein in induced sputum and blood: effects of budesonide and terbutaline treatment. Ann Allergy Asthma Immunol. 2002; 89(5): 492–497, doi: 10.1016/s1081-1206(10)62087-x, indexed in Pubmed: 12452208.
36. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA), Update 2019. Dostępne na stronie: https://ginasthma.org/gina-reports/. [dostęp: 11.10.2019].
37. Taylor TE, Zigel Y, De Looze C, et al. Advances in audio-based systems to monitor patient adherence and inhaler drug delivery. Chest. 2018; 153(3): 710–722, doi: 10.1016/j.chest.2017.08.1162, indexed in Pubmed: 28887061.
38. Blakey JD, Bender BG, Dima AL, et al. Digital technologies and adherence in respiratory diseases: the road ahead. Eur Respir J. 2018; 52(5), doi: 10.1183/13993003.01147-2018, indexed in Pubmed: 30409819.
39. PROAIR® DIGIHALERTM (albuterol sulfate) inhalation powder. Dostępne na stronie: www.proairdigihaler.com/globalassets/proair_digihaler/Proair_Digihaler_PI.pd. [Dostęp: 10.06.2019 r.].
40. Salbutamo. Dostępne na stronie: www.mp.pl/pacjent/leki/subst.html?id=711. [Dostęp: 14.12.2019 r.].
41. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Clinical Practice Guidelines. National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. Bethesda (MD): National Heart, Lung, and Blood Institute (US); 2007 Aug. Report No.: 07-4051. Dostępne na stronie: www.nhlbi.nih.gov/NHLBAC-Asthma-WG-Report.pdf. [Dostęp: 12.02.2018 r.].
42. Travers A.H., Milan S.J., Jones A.P. i wsp. Addition of intravenous beta(2)-agonists to inhaled beta(2)-agonists for acute asthma. Cochrane Database Syst Rev. 2012; 12: CD010179, doi: 10.1002/14651858.CD010179, indexed in Pubmed: 23235685.
43. Emeryk A., Emeryk-Maksymiuk J. Połączenie krótkodziałającego b2-mimetyka z krótkodziałającym lekiem antycholinergicznym u dzieci z obturacją oskrzeli. Terapia. 2018; 26: 4.
44. Emeryk A., Pirożyński M., Mazurek H. i wsp. Polski Przewodnik Inhalacyjny. Via Medica, Gdańsk 2015: 1–22.

45. Pollock M., Sinha I.P., Hartling L. i wsp. Inhaled short-acting bronchodilators for managing emergency childhood asthma: an overview of reviews. Allergy. 2017; 72(2): 183–200, doi: 10.1111/all.13039, indexed in Pubmed: 27588581.
46. Emeryk A., Doniec Z., Mazurek H. i wsp. Zasady stosowania komór inhalacyjnych u dzieci. Pediatria Polska. 2017; 92(3): 288–293, doi: 10.1016/j.pepo.2017.02.003.
47. Boshra M.S., Almeldien A.G., Salah Eldin R. i wsp. Total emitted dose of salbutamol sulphate at different inhalation flows and inhalation volumes through different types of dry powder inhalers. Exp Lung Res. 2018; 44(4-5): 211–216, doi: 10.1080/01902148.2018.1489015, indexed in Pubmed: 30346848.
48. Emeryk A., Bodajko-Grochowska A., Bartkowiak-Emeryk M. Postępowanie ambulatoryjne w zaostrzeniach astmy u dzieci poniżej 6. roku życia. Między standardami a życiem. Standardy Medyczne/Pediatria. 2017; 14: 808–818.
49. Lin A.T., Moore-Clingenpeel M., Karsies T.J. Comparison of two continuous nebulized albuterol doses in critically ill children with status asthmaticus. J Asthma. 2019 [Epub ahead of print]: 1–7, doi: 10.1080/02770903.2019.1623249, indexed in Pubmed: 31119958.
50. Rodrigo G. Asthma in adults (acute). BMJ Clin Evid. 2011; 4: 1513.
51. Lin Y.Z., Huang F.Y. Comparison of breath-actuated and conventional constant-flow jet nebulizers in treating acute asthmatic children. Acta Paediatr Taiwan. 2004; 45(2): 73–76, indexed in Pubmed: 15335114.
52. Lipworth B.J., Sims E.J., Taylor K. i wsp. Dose-response to salbutamol via a novel palm sized nebuliser (Aerodose Inhaler), conventional nebuliser (Pari LC Plus) and metered dose inhaler (Ventolin Evohaler) in moderate to severe asthmatics. Br J Clin Pharmacol. 2005; 59(1): 5–13, doi: 10.1111/j.1365-2125.2005.02168.x, indexed in Pubmed: 15606434.
53. Ducharme F.M., Dell S.D., Radhakrishnan D. i wsp. Diagnosis and management of asthma in preschoolers: A Canadian Thoracic Society and Canadian Paediatric Society position paper. Can Respir J. 2015; 22(3): 135–143, doi: 10.1155/2015/101572, indexed in Pubmed: 25893310.
54. Hartman S., Merkus P., Maseland M. i wsp. Hypokalaemia in children with asthma treated with nebulised salbutamol. Arch Dis Child. 2015; 100(10): 970–972, doi: 10.1136/archdischild-2015-308427, indexed in Pubmed: 26044135.
55. Global Strategy for the Diagnosis, Management, andPrevention of Chronic Obstructive Pulmonary Disease 2020 Report. Dostępne na stronie: https://goldcopd.org/wp-content/uploads/2019/11/GOLD-2020-REPORT-ver1.0wms.pdf. [Dostep: 14.01.2020 r.].
56. van Geffen WH, Douma WR, Slebos DJ, et al. Bronchodilators delivered by nebuliser versus pMDI with spacer or DPI for exacerbations of COPD. Cochrane Database Syst Rev. 2016(8): CD011826, doi: 10.1002/14651858.CD011826.pub2, indexed in Pubmed: 27569680.
57. Bardsley G, Pilcher J, McKinstry S, et al. Oxygen versus air-driven nebulisers for exacerbations of chronic obstructive pulmonary disease: a randomised controlled trial. BMC Pulm Med. 2018; 18(1): 157, doi: 10.1186/s12890-018-0720-7, indexed in Pubmed: 30285695.
58. Doniec Z., Mastalerz-Migas A., Bręborowicz A. i wsp. Rekomendacje postępowania w astmie wczesnodziecięcej dla lekarzy Podstawowej Opieki Zdrowotnej — KOMPAS POZ. Fam Med Prim Care Review. 2016; 8: 81–92.
59. Ventolin. Charakterystyka produktu leczniczego. Dostępne na stronie: http://leki.urpl.gov.pl/files/25_Ventolin_aerozol_inh_zaw.pdf. [dostęp: 14.12.2019].
60. Gadomski AM, Scribani MB. Bronchodilators for bronchiolitis. Cochrane Database Syst Rev. 2014(6): CD001266, doi: 10.1002/14651858.CD001266.pub4, indexed in Pubmed: 24937099.
61. Dunn M, Muthu N, Burlingame CC, et al. Reducing albuterol use in children with bronchiolitis. Pediatrics. 2020; 145(1), doi: 10.1542/peds.2019-0306, indexed in Pubmed: 31810996.
62. Bar-Aluma BE, Efrati O, Kaufmann H, et al. A controlled trial of inhaled bronchodilators in familial dysautonomia. Lung. 2018; 196(1): 93–101, doi: 10.1007/s00408-017-0073-7, indexed in Pubmed: 29234869.
63. Barry PJ, Flume PA. Bronchodilators in cystic fibrosis: a critical analysis. Expert Rev Respir Med. 2017; 11(1): 13–20, doi: 10.1080/17476348.2017.1246358, indexed in Pubmed: 27718752.
64. Knight-Madden J, Hambleton I. Inhaled bronchodilators for acute chest syndrome in people with sickle cell disease. Cochrane Database of Systematic Reviews. 2016, doi: 10.1002/14651858.cd003733.pub4.
65. Melo SM, Oliveira LA, Rocha RD, et al. Bronchodilator test in extreme old age: Adverse effects of short-acting beta-2 adrenergic agonists with clinical repercussion and bronchodilator response. Rev Assoc Med Bras (1992). 2019; 65(11): 1343–1348, doi: 10.1590/1806-9282.65.11.1343, indexed in Pubmed: 31800894.